World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

EFFECT OF VITAMIN D AND MELATONIN SUPPLEMENTATION AS ADJUVANT IN TREATMENT OF NEONATAL JAUNDICE

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Article Received on 25/12/2019 **Article Revised on 15/01/2020** **Article Accepted on 05/02/2020**

ABSTRACT

In newborn babies and neonates, neonatal jaundice is a common problem which is treated by different methods to avoid the development of complication especially bilirubin encephalopathy or kernicterus. This prospective clinical trial was done during the period from July 2016 to January 2018 in Al-Karama hospital in Baghdad/Iraq on 120 neonates suffering from neonatal jaundice. The studied neonates were divided into 3 groups: Group (1) who were treated by vitamin D and phototherapy, group (2) who were treated by melatonin and phototherapy and group (3) who were treated by phototherapy alone. Results showed that serum bilirubin was significantly declined in neonates of group (1) who were treated by vitamin D and phototherapy, compared with neonates of group (2) and (3) who were treated with combined melatonin with phototherapy and phototherapy respectively with p-value equal 0.002 and 0.001 respectively. There was a significant decrease in serum bilirubin levels in neonate of group (2) who were treated with melatonin and phototherapy when compared with group (3) who was treated by phototherapy alone with p-value equal 0.002. It can be concluded that Vitamin D and melatonin could be used as adjuvant treatments in neonatal jaundice in combination with phototherapy with superiority of vitamin D over melatonin.

KEYWORDS: Neonates, Jaundice, Vitamin D, Melatonin.

INTRODUCTION

One of the most important health problems in neonates is the neonatal jaundice or neonatal indirect hyperbilirubinemia which is a very common condition all over the world especially when the levels of indirect bilirubin increased to levels that could pass the blood brain barrier leading to bilirubin encephalopathy or kernicterus if untreated as early as possible.[1] The neonatal jaundice is defined clinically as yellow color of the skin of the body and also the mucus membrane, in addition to the eyes especially the sclera due to the rise of the serum bilirubin levels. It is either physiological which does not rise to high levels or pathological which rises to high levels. Pathological jaundice may be affected by different parameters such as gestational age, birth weight, premature rupture of membranes, maternal infectious disorders or other diseases during pregnancy.[1]

There are numerous reasons for the occurrence of neonatal jaundice or neonatal hyperbilirubinemia including blood group incompatibility, Rh incompatibility, glucose-6-phosphate dehydrogenase deficiency and elevated red blood cells mass. Several treatment modalities are used to manage pathological jaundice in neonates including phototherapy, exchange blood transfusion and intravenous immunoglobulin but there are many side effects to these lines of treatment in addition to difficulties and serious risks of some lines of treatment especially the exchange blood transfusion. So, the need of new lines of treatment that could be used as adjuvant therapies to the previous old established lines of treatment of neonatal jaundice have become essential to protect the neonates from the serious effect of increased levels of bilirubin which may lead to bilirubin encephalopathy or kernicterus.[2]

Vitamin D is a fat-soluble vitamin which has an important function in the body especially in the teeth and bone formation in infants and children. The liver plays a very important role in the synthesis of vitamin D in neonates and also the liver plays a major role in bilirubin metabolism by conversion of unconjugated bilirubin

which could pass the blood brain barrier to conjugated bilirubin.[3]

In addition, the 25-hydroxylation phase, one of the core phases of vitamin D biosynthesis occurs in the liver as well as bilirubin conjugation.[4] Melatonin is a physiological indoleamine which is secreted from the pineal gland into the blood. This hormone has antioxidant effects; it is synthesized mainly in the pineal gland from the amino acid tryptophan. Melatonin has a marvelous effect in prevention and treatment of liver injuries and diseases by its antioxidant effect which protects the liver from the hazardous effects of these oxidants.[5] The liver action includes detoxification of large amounts of reactive oxygen species which are generated in the body and they exert a toxic effect on hepatocytes. A valuable and beneficial antioxidant action which is done by melatonin and has an important role in prevention of the toxic effects of these oxidants like oxygen free radicals on the liver. The healthy liver also is the site for detoxification and conjugation of the indirect bilirubin to direct bilirubin.[6] The aim of this research is to study the role of vitamin D and melatonin supplementation as adjuvant therapies in cases of neonatal jaundice.

PATIENT AND METHODS

This current prospective clinical trial was done during the period from July 2016 to January 2018 in Al-Karama teaching hospital in Baghdad/Iraq on 120 neonates suffering from neonatal jaundice. The studied neonates were divided into 3 groups as follows: Group (1) included (40) full term neonates admitted with indirect hyperbilirubinemia from 14-20 mg/dl at the 3rd day of life who received phototherapy and also received 10 drops of vitamin D (1000 IU) once daily for 5 days in the form of Vidrop® (Medical Union Pharmaceuticals, Egypt).[7] Group (2) included (40) full term neonates admitted with indirect hyperbilirubinemia from 14-20 mg/dl at 3rd day of life who received phototherapy and also received melatonin in a dose of 10 mg/kg once daily for 5 days. Melatonin tablets (3mg per tablet; Puritan's Pride®, Oakdale, NY, USA) were crushed, then dissolved in 5ml of distilled water and administered via orogastric tube.[8] Group (3) included (40) full term neonates admitted with indirect hyperbilirubinemia from 14-20 mg/dl at 3rd day of life who received phototherapy only.

The inclusion criteria involved full term neonates who were admitted to the incubator at the third day of life were suffering from indirect hyperbilirubinemia with total serum bilirubin from 14-20 mg/dl. All the (3) groups were treated with phototherapy in addition to vitamin D and melatonin in groups (1) and (2) respectively.

The exclusion criteria involved preterm neonates, conjugated hyperbilirubinemia, neonatal sepsis, neonatal hypoxia, neonatal respiratory distress, congenital anomalies, liver or kidney disease in the neonates or their mothers.

Venous blood samples were taken from each neonate using a sterile BD vacutainer butterfly needle. Each blood sample was divided into two portions (2 ml each). The first portion was collected in a tube containing (EDTA) for reticulocytes count and hemoglobin level determination. The second portion was collected in a BD vacutainer serum separator tube, and serum samples were separated after centrifugation and stored at -20°C until total bilirubin levels were measured.

Reticulocytes percent and hemoglobin levels were assayed using an automated hematology analyzer (Sysmex® XT1800I, Japan). Serum total bilirubin was measured, according to the manufacturer's instructions (Roche® Diagnostics, Germany) using the colorimetric method.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS) version 21. Data were expressed as mean ± SD. Statistical comparison among Groups was performed by ANOVA test, Chi-square (X^2) test for comparison between two Groups. Statistical significance was set at p-values <0.05.

RESULTS

Comparison between the (3) groups in regard to weight (kg), gestational age (Weeks), bilirubin levels (mg/dl), hemoglobin levels (gm/dl), reticulocyte count (%), mode of delivery and sex showed no significant differences as shown in table (1).

Table (1): Comparative characteristics between the studied groups on admission (3rd day of life).

Variables		Group 1 (n=40)		Group 2 (n=40)		Group 3 (n=40)		F-test	p-value
Weight (g)	Mean±SD	3675.5 ± 110.0		3661.3 ± 105.0		3625.1 ± 100.0		2.410	0.094
Gestational Age (Weeks)	Mean±SD	39.2 ± 1.1		39.3 ± 1.0		39.1 ± 1.2		0.329	0.720
Bilirubin levels (mg/dl)	Mean±SD	17.35± 4.6		17.65 ± 4.2		17.45 ± 3.7		0.053	0.948
Hemoglobin levels (gm/dl)	Mean±SD	14.1 ± 0.9		14.3 ± 0.9		14.2 ± 1.0		0.458	0.634
Reticulocyte count (%)	Mean±SD	7.56 ± 0.56		7.45 ± 0.85		7.55 ± 0.75		0.278	0.758
Variables		**N**	**%**	**N**	**%**	**N**	**%**	**X^2**	**p-Value**
Mode of delivery	NVD	18	45	15	38	13	33	1.34	0.512
	CS	22	55	25	62	27	67		

Sex	Male	16	40	22	55	17	43	2.081	0.353
	Female	24	60	18	45	23	57		

*P-value is significant if < 0.05 NVD: Normal Vaginal Delivery. CS: Cesarean Section.

Table (2) showed the comparison between admission and after 7 days in the three groups. There was a significant difference in bilirubin levels before and after 7 days in the three groups separately.

Table (2): Comparison of the studied groups in regard to serum bilirubin on admission and at 7 days of admission.

Variables		**At 3rd day of life (1st day of admission)**	**At the 10th day of life (7th day of admission)**	**t.-test**	**p-value**
Serum bilirubin (mg/dl)	Group 1	17.35± 4.6	7.9 ± 1.1	12.637	0.001
	Group 2	17.65 ± 4.2	7.4 ± 1.0	15.01	0.001
	Group 3	17.45 ± 3.7	9.2 ± 1.4	13.19	0.001
p-value is significant if <0.05.					

Comparison between the (3) groups regarding serum bilirubin from the 2nd to the 6th day of admission demonstrated no significant differences between the 3 groups in the 2nd, 3rd and 4th day of admission, while significant differences were observed between the (3) groups in the 5th and 6th day of admission as illustrated in table (3).

Table 3. Comparison between group 1, 2 and 3 regarding serum bilirubin between the 2nd and 6th day of admission.

Variables	**Group 1**	**Group 1**	**Group 1**	**F-test**	**p-value**
Time (Days)	**Serum bilirubin (mg/dl)**				
2nd day of admission	15.3 ± 2.9	15.8 ± 1.9	15.5 ± 3.2	0.341	0.711
3rd day of admission	14.1 ± 2.1	14.4 ± 2.1	14.9 ± 1.9	1.577	0.211
4th day of admission	12.3 ± 2.5	13.1 ± 1.7	13.4 ± 2.6	2.440	0.092
5th day of admission	10.9 ± 1.3	11.6 ± 1.2	12.1 ± 1.1	10.046	0.001
6th day of admission	9.0 ± 1.3	9.7 ± 1.1	10.6 ± 1.2	17.788	0.001
p-value is significant if <0.05.					

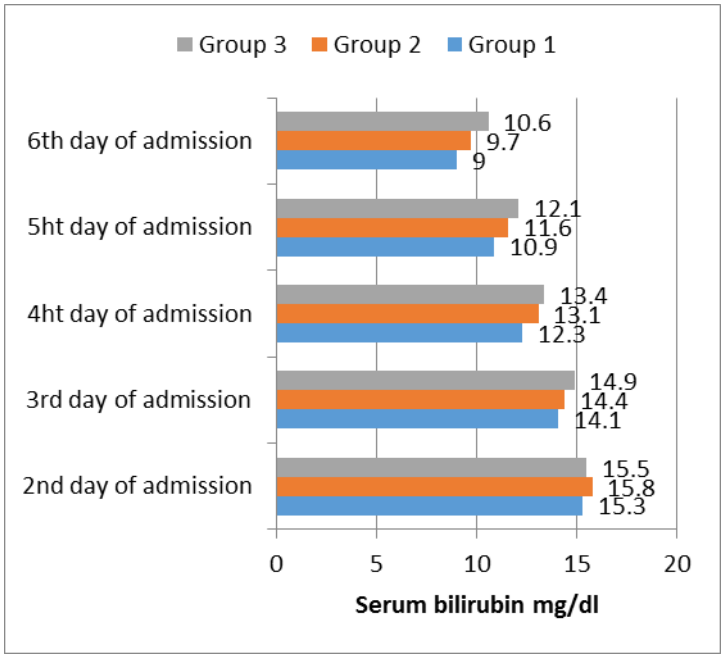
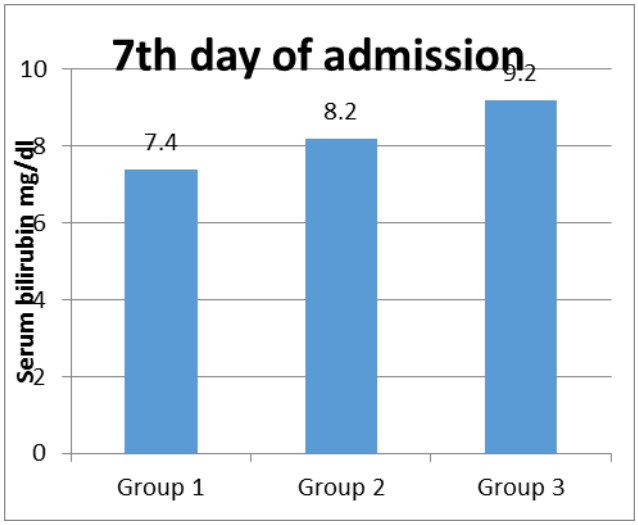


Table (4) showed that in regard to serum bilirubin at the 7th day of admission, there were significant differences between the groups with p-value = 0.001, while there was a significant difference between group (1) and group (3) with p-value = 0.001, with a significant difference between group (2) and group (3) at p-value = 0.002, and

a significant difference between group (1) and group (2) at p-value = 0.002 as shown in table (4).

Table (4): Comparison between group 1, 2 and 3 regarding serum bilirubin at the 7th day of admission.

Serum bilirubin (mg/dl) at the 7th day of admission	Group 1 (n=40)	Group 2 (n=40)	Group 3(n=40)
Mean ± SD	7.4 ± 1.0	8.2 ± 0.9	9.2 ± 0.5
F-test	47.379		
p-value	0.001*		
Group 1 and Group 2	Group 1 and Group 3		Group 2 and Group 3
0.002*	0.001*		0.002*
*p-value is significant if <0.05.			



DISCUSSION

Neonatal jaundice or neonatal indirect hyperbilirubinemia is a common disease in neonates which is caused by many different causes. The neonatal jaundice may be physiological or pathological causing many serious problems especially bilirubin encephalopathy or kernicterus which has many dangerous squeals like cerebral palsy, mental retardation, deafness and permanent brain damage.[9] The treatment of pathological neonatal jaundice had some side effects especially the exchange blood transfusion which may cause thrombosis, hemorrhage, transmission of diseases and serious reactions from the exchanged blood, so there may be a need for searching about some adjuvant therapies that could be used as an adjuvant therapy with phototherapy which is used in the treatment of pathological neonatal jaundice.[10]

This study revealed that vitamin D administration to neonates with pathological neonatal jaundice was accompanied by improvement in the levels of serum bilirubin and the group which is treated with vitamin D and phototherapy was accompanied by significant decrease in the levels of the serum bilirubin if compared with group which is treated by phototherapy alone which may indicate that vitamin D is important in the reduction of serum bilirubin in neonates with pathological jaundice. In agreement with our study, there was a study which stated that levels of serum vitamin D in neonates were significantly lower in neonates with pathological jaundice when compared with the control non-jaundiced group which may indicate a strong relationship and significant negative correlation between the levels of serum bilirubin and serum vitamin D levels in neonates.[11]

Vitamin D was proven to play an important role in liver metabolism through hydroxylation of vitamin D in the liver. The liver tissue is the cornerstone for activation of vitamin D through hydroxylation of Cholecalciferol which is converted in the liver to calcifediol (25-hydroxycholecalciferol) and also the liver is responsible for the synthesis and conjugation of bilirubin. Some studies revealed that the decreased serum levels of vitamin D might be associated with the occurrence of neonatal jaundice.[6]

Although the pathway of metabolism of vitamin D and bilirubin are performed on two pathways, both pathways had a common pathway in the liver and the presence of good supplementation of vitamin D will help the liver metabolism and the changes in metabolism or synthesis of each of them might have an impact on the metabolism and the synthesis of the other.[12] There was a study which stated that there was no relationship between the neonatal serum vitamin D levels and neonatal indirect hyperbilirubinemia on contrary to our result which

revealed that vitamin D administration with phototherapy to pathologically jaundiced neonates was associated with significant decrease in serum bilirubin in neonates if compared to neonates who were treated by phototherapy alone.[13] This study tried to detect the effect of melatonin administration by the neonates on the levels of serum neonatal bilirubin and explain if the melatonin could help in the reduction of serum bilirubin in neonates suffering from pathological neonatal jaundice.

Melatonin administration had various and multiple advantages and benefits in liver functions and the melatonin which prevents the oxidative stress and supports the liver functions including bilirubin metabolism and conjugation of unconjugated or indirect bilirubin to conjugated or direct bilirubin though decreasing the indirect hyperbilirubinemia.[5] Melatonin has an important role in improvement of hepatic microcirculation, and melatonin administration has many protective effects on liver tissues and promotes adequate liver functions including bilirubin metabolism.[14]

Melatonin is mainly accumulated in high concentrations in the liver, and the metabolism of the melatonin occurs only in the liver and also the bilirubin metabolism occurs in the liver and the changes in metabolism of each of them might have an impact on the metabolism of the other. Melatonin acts as potent and effective antioxidants that helps in protecting liver tissues and maintaining the liver functions including bilirubin metabolism which help in reducing indirect bilirubin levels in the serum by bilirubin conjugation, and fortunately the melatonin metabolites also have potent and good anti-oxidative function which help in more protection of liver tissues structure and function. The melatonin does its anti-oxidative effects either through its radical scavenging functions or via activation of antioxidant enzymes.[15]

The liver plays an important role in the metabolism and detoxification of various substances in the body. During the metabolism and detoxification of some substances there will be production of reactive oxygen species which produce a toxic effect on hepatotoxic effects which affect the liver function in the metabolism of various substances like bilirubin metabolism, and the melatonin which is a potent antioxidant through various mechanisms will protect the liver tissues and maintaining excellent liver functions.[16]

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